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Functional Imaging-guided Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer: Review

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ABSTRACT

In treating locally advanced non-small-cell lung cancer (NSCLC), radio-tolerance of the normal lung often limits the amount of dose that can be delivered to the primary cancer site. Radiation-related pneumonitis (RP) and other normal lung tissue complications have a significant impact on clinical outcome and patient quality of life. How to minimize treatment side effects while achieving desirable local control of lung cancers has been a continuous challenge.

Functional imaging-guided radiotherapy, which can achieve a local boost of primary cancer site or functional avoidance of normal organs, has been increasingly utilized in clinics. Various imaging approaches have been employed to achieve functional imaging guidance and implemented in different treatment regimens. There are several on-going clinical trials aiming to evaluate the clinical outcomes that are utilizing functional imaging-guided photon radiation to spare the high functioning portions of the lungs. The main applications of functional imaging-guided radiotherapy in the management of NSCLC patients will be discussed in this review.

Introduction

Radiotherapy plays a major role in the treatment of patients with locally advanced non-small-cell lung cancer (NSCLC), primarily due to the extent of the disease not suitable for surgery. Despite advances in local and systemic therapies, local control and survival remain poor and there is a sense that a therapeutic plateau has been reached with conventional approaches. On the contrary, strategies for dose escalation have shown encouraging results with improved therapeutic ratio and survival as confirmed by Radiation Therapy Oncology Group (RTOG) 9311 and several other clinical trials[1,2]. However, the radio-tolerance of the normal lung is the primary limiting factor of the dose escalation to the primary cancer site. Therefore, one proposal to minimize the radiation-induced lung injury is to take consideration of the pulmonary function by deliberately reducing dose to highly functional regions when generating the treatment plan. This concept of functional imaging-guided lung avoidance treatment has been investigated with several imaging modalities, including single photon emission computed tomography (SPECT), hyperpolarized (HP) gas magnetic resonance imaging (MRI), and increasingly with 4-dimensional (4D) computed tomography (CT) based measures of lung function. Here we review the applications with different functional imaging modalities and different treatment modalities.

Functional Lung Imaging Modalities

Lung function can be evaluated by functional imaging modalities such as SPECT[3,4], HP Helium or Xenon MRI[5,6] and 4D CT ventilation imaging[7-9].

Perfusion SPECT has long time been the most commonly used imaging modality for functional lung assessment[3,4]. The ventilation map generated by SPECT can be further utilized to optimize beam directions for radiation treatment planning to potentially spare highly functional normal lung[3,10]. However, SPECT has limitations with low spatial and temporal resolution compared to anatomical imaging as CT or MRI. It also suffers from the potential errors in photon attenuation and scatters correction, imaging registration to CT for planning, and patient repositioning or setup inconsistency[11]. Recently HP gas MRI has been developed rapidly, including helium-3[5] with stronger signals due to higher levels of polarization and higher gyromagnetic ratio, and xenon-129[6], with an unlimited supply in nature and its falling cost, providing a unique tool for direct assessment of lung ventilation[12]. But in general, functional MRI is not yet widely available in clinics, and the routine application in clinical practice would be associated with long scanning time and high cost to patients[13].

CT especially 4D-CT, on the contrary, is gaining its popularity to assess the pulmonary function due to the wide accessibility, routine clinical application, and low cost. Previous literature has detailed the methodology of deriving pulmonary ventilation maps from 4D-CT[7,9]. Typically, a deformable image registration (DIR) is involved to obtain a displacement vector field (DVF) from peak-exhale to peak-inhale phases from the 4D series. With the assumptions that regional ventilation is proportional to the regional volume change, either Hounsfield unit (HU) change[14-16] or Jacobian measurement[7,17,18] of the DVF can be used to derive ventilation map. Currently, various DIR algorithms have been developed and tested, of which the transformation model ranges in complexity from a simple extension of a global affine transformation to a completely local or free-form model where each voxel in the image can move independently. Also, there are two classes of similarity metrics commonly used to regulate DIR performance: geometry-based or intensity-based. As 4D-CT pulmonary ventilation images can vary widely with DIR algorithms and metrics, careful validation is needed before the clinical use. Cui *et al*. have evaluated 7 different DIR algorithms in generating 4D-CT based lung ventilation maps and compared the results with what is captured by HP gas tagging MRI on three healthy patients[19]. A large number (300-500) of uniformly distributed landmarks were identified to enable a complete assessment of DIR throughout the entire lung. The 7 DIR method platforms included Velocity, MIM, Mirada, Elastix and 3 other in-house built algorithms from DIRART toolbox such as Double Force Demons, Improved Lucas-Kanade, and Iterative Optical Flow. Among all algorithms, the Jacobian derivation of the deformable vector fields (DVFs) generated from Velocity (multi-pass free-form deformation) gave the most reasonable result. Brennen *et al*. performed clinical validation by comparing using HU-based and Jacobian-based 4D-CT ventilation metrics with pulmonary function test data on ninety-eight lung cancer patients[20]. They confirmed HU-based ventilation metrics produced better correlations when compared to Jacobian-based ventilation metrics. There are also several studies attempting to validate 4DCT-ventilation by comparing it against other ventilation imaging modalities such as nuclear medicine ventilation-perfusion imaging[21], xenon-CT[4,17], PET[22], and MRI[23,24] or directly with pulmonary function testing[20]. The studies generally found good agreement on a global level, yet the regional physiologic accuracy has not been validated in patients. In addition, temporal changes in regional ventilation to a segment of lung previously impaired by compression from a local tumor might occur during the course of radiation treatment. A possible explanation of these changes is that the shrinkage of lung tumor in response to radiation might increase the ventilation due to the reopening of the airways[25]. Nevertheless, additional work is needed to validate the regional physiologic accuracy of 4DCT derived ventilation imaging in real patients especially during the course of radiation treatment.

Implementations with Photon Radiotherapy

The feasibility of photon treatment planning using an optimal beam arrangement aiming at preserving the high functioning portion of the lung under the guidance of functional imaging has been widely studied. Studies have demonstrated decreasing the radiation dose to high-functioning lung areas and directing the radiation to the parts with inactive perfusion/ventilation may help to protect highly functioning lung regions and thus reduce the incidence and seriousness of radiation pneumonitis (RP)[7,8,26-30]. Those treatment plans did not compromise the DVHs of OARs, such as the spinal cord, esophagus, and heart, which may be additional important clinical factors. These results also demonstrated that functional imaging could be applied safely to photon radiation treatments for patients with NSCLC, without exceeding the dose-volume tolerances of OARs.

In addition, Ireland *et al*. showed that patients with specific types of functional defects, tumor volumes and positions will benefit from the inclusion of functional data for normal lung dose reduction[31]. Lavrenkov *et al*. compared IMRT planning and 3D-CRT planning using functional SPECT perfusion images and demonstrated that IMRT planning led to a lower high functioning lung mean dose than 3D-CRT planning[32]. Yamamoto *et al*. demonstrated that 4D-CT ventilation imaging based functional IMRT and

VMAT treatment planning, by changing only one variable (i.e., absence/presence of constraints on the functioning lung), led to significant reductions in the high functioning lung dose[27]. Faught *et al.* discussed which dose-function metrics should be used for treatment planning and aimed to construct most predictive models to predict RP[33].

There are several on-going clinical trials, such as NCI NCT02308709, NCT02528942, and NCT02843568, that utilize functional imaging-guided photon radiation to spare higher functioning portions of the lung and aim to evaluate the clinical outcome. With this technique of functional lung sparing, the goal is to reduce the rates of lung parenchymal toxicity, i.e. pneumonitis, and to further allow for dose escalation.

Implementations with Proton Radiotherapy

To date, most of the work utilizing functional imaging was done with photon-based radiotherapy and limited work was reported with proton treatment. The energy deposition of protons has theoretical advantages because of the physical property of proton particles, which can be exploited to reduce exposure of normal tissues to radiation, particularly to reduce low dose radiation exposure to OARs. Under this premise, emerging dosimetric and clinical studies are being undertaken to assess the role of proton radiotherapy vs. photon and the potential to further escalate dose with proton treatment[34-38].

Our group, is the first to demonstrate the feasibility of incorporating 4DCT-based ventilation map into proton planning with both double scattering (DSPT) and pencil scanning (IMPT) techniques[39]. The results showed that both DSPT and IMPT plans gave a superior dosimetric advantage over photon IMRTs in sparing low dose regions of the total lungs in terms of V5 (volume receiving ≥ 5Gy). The functional planning in IMPT delivery can further reduce the low dose in high functioning lung without degrading the PTV dosimetric coverage or increasing dose to critical structures. Yet, the functional DSPT only showed marginal benefit in sparing high-functioning lung in terms of V5 or V20 (volume receiving ≥ 20Gy) compared to anatomical plans. Recently, O'Reilly *et al*. conducted a case-control study on 48 NSCLC patients to compare the high-ventilation lung dose with RP outcome[40]. Their data supported findings that dose to the high-ventilated lung may serve as a predictor of RP regardless treated with photons or protons.

To our best knowledge, functional imaging-guided proton treatment with normal lung avoidance is still very new and no clinical trial has been conducted so far. With the rapid growth of proton centers and advances in imaging techniques, there will be more interests in applying functional imaging in proton planning. However, for lung proton treatment especially pencil beam delivering, several practical issues remain. For the IMPT technique, one of the major concerns comes from the interplay effects between the moving beams and moving tissue. The magnitude of the interplay effect with scanning proton beams has been reported in previous studies, and it has been shown that proton dose could be impacted enormously by the interplay effect for tumor motions around or larger than 10 mm[41-45]. Kardar *et al*. introduced a 4D dynamic dose simulator and further investigated the impact of motion pattern and starting phases on the interplay effects[46,47]. They observed situations in which motion more than 5 mm and small tumor sizes led to relatively large uncertainties caused by the interplay effect in a single fraction. In contrast, for some patients with motion less than 5mm and large tumor size, the interplay effect was small. Moreover, a recent study by Inoue *et al*. evaluated the impact of setup and range uncertainties, breathing motion, and interplay effects in IMPT dose distributions[48]. Their results demonstrated that in robust-optimized plans the dosimetric effects due to geometric and radiologic variation had a limited impact on target coverage, target dose homogeneity, and OAR dose parameters when treated with multi-fractionation clinical scheme. As such for future functional imaging-guided IMPT delivery, it is very critical to identify a proper patient cohort. It might be appropriate to include only patients with non-small size tumor and also with breathing motion less than 5-7 mm. In addition, as suggested by Kardar *et al*. and Li *et al*.[46,47], a target coverage difference between the maximum in-hale (CT0) and maximum ex-hale (CT50) needs to be assessed and a less than 5% difference may suggest a robust coverage. Nevertheless, further studies are needed to ensure the robustness of the proton treatment for moving target.

Conclusion

This review highlights the inclusion of normal lung functional data into treatment planning using photon or proton radiation for lung cancer. It is feasible to use functional imaging techniques to obtain the perfusion/ventilation imaging to assess the normal lung function and then optimize the treatment planning by limiting dose to the functional lung regions. The benefit is to minimize the risk of radiation-induced lung injury, which may potentially allow dose escalation and thereby improve overall survival. Several clinical trials with photon treatment are on-going and similar studies are expected to extend to proton treatment. However, beyond the question regarding which imaging or treatment modality should be used for functional imaging-guided radiation treatment, the clinical implication underlying the modification of the dose for functional lung should be investigated. The clinical assumption for dose-redistribution to avoid high-functional lung is that a higher dose can be targeted to low perfused/ventilated lung. Lung function can be reduced irreversibly by radiation, but tumor itself can be responsible for reduced lung function. Therefore, a potential limitation of normal lung avoidance is that lung volumes that may have received a functionally modified, amplified dose may regain some degree of function after treatment. Hence, whether defects are permanent or reversible becomes an important issue when assigning functional and non-functional planning constraints. Further validation tests, planning studies and clinical trials will be required to increase our understanding of the potential benefits and long-term effects of functional imaging-guided lung avoidance planning strategies.

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